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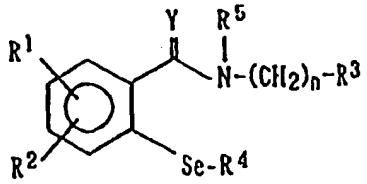
(54) Title: THERAPEUTIC ANTI-ASTHMA AGENTS CONTAINING SELENIUM COMPOUNDS

(54) Bezeichnung: THERAPEUTISCHE MITTEL, ENTHALTEND ORGANISCHE SELENVERBINDUNGEN GENGEN ASTHMA

(57) Abstract

The description relates to a therapeutic agent which comprises as the active agent a compound given by the formula (1) and/or (1') and/or a pharmaceutically acceptable salt thereof. The agent of the invention exhibits great effectiveness in cases of both immediate and later asthmatic reactions, especially the latter. Owing to its low toxicity, the agent of the invention can safely be prescribed for human beings.



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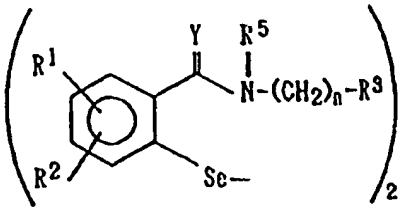

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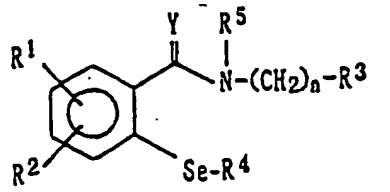
(57) Zusammenfassung

Es wird ein therapeutisches Mittel beschrieben, das als Wirkstoff eine Verbindung, die durch die nachfolgende Formel (1) und/oder (1') wiedergegeben ist, und/oder ein pharmazeutisch akzeptables Salz dieser Verbindung umfaßt. Das erfindungsgemäße Mittel zeigt hohe Wirksamkeiten sowohl in bezug auf die unmittelbaren als auch späten asthmatischen Reaktionen und insbesondere auf die späten asthmatischen Reaktionen. Bedingt durch die geringe Toxizität kann das erfindungsgemäße Mittel sicher beim Menschen dargereicht werden.

ABSTRACT OF THE DISCLOSURE

The present invention provides a safe therapeutic agent for asthma which suppresses both immediate and late asthmatic responses in bronchial asthma. The therapeutic agent of the invention comprises, as an active component, a compound represented by the following formula (1) or (1'):



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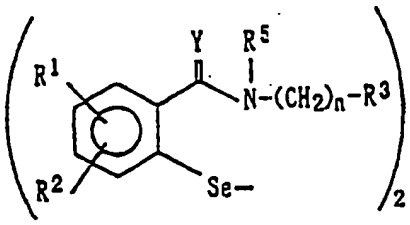

(1')

or a pharmaceutically acceptable salt of the compound. The agent of the invention shows highly effects on both immediate and late asthmatic responses, and particularly on late asthmatic responses. The agent can be safely administered to humans as it has low toxicity.

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THERAPEUTIC AGENTS FOR ASTHMA

BACKGROUND OF THE INVENTION

Field of the Invention:

The present invention relates to therapeutic agents for asthma that effectively suppress asthmatic responses, especially late asthmatic responses, in bronchial asthma.

Description of the Related Art:

In general, bronchial asthma has been recognized as a disease which is characterized by contraction of smooth muscles in the airway due to type I anaphylaxis. However, recent advances in the research in this field have revealed a part of the pathogenesis of asthma, which is characterized by reversal airflow limitation, airway inflammation, mucus hypersecretion and remodeling of the airway structure due to chronic inflammation. Pharmacologic therapy should be established beyond understanding of such pathogenesis.

At present available medications for asthma are relievers to reverse airflow limitation like as a beta-agonist and controllers to prevent symptoms by means of suppressing airway inflammation such as a corticosteroid inhalant. A beta-agonist acts quickly to relieve bronchoconstriction and its acompanying symptoms like cough, chest tightness and wheezing. An inhaled corticosteroid used daily on a long term basis to achieve and maintain control of persistent asthma.

However, beta-agonists have a few adverse effects such as cardiovascular stimulation, skeletal muscle tremor, hypokalemia and irritability. On the other hand, an inhaled corticosteroid

potentiates oropharyngeal candidiasis, dysphonia and occasional coughing from upper-airway irritation in spite that the risk for systemic effects of an inhalant is less than systemic corticosteroids. Long term use of oral or parenteral corticosteroids can cause serious adverse effects like as osteoporosis, arterial hypertension, diabetes, hypothalamic-pituitary-adrenal axis suppression, cataracts, obesity, skin thinning leading to cutaneous striae and easy bruisability, and muscle weakness. Controller agents are administered for a long period, and therefore the systemic side effects of those agents should be avoided or minimized.

From the concept that controller agents should have minimal adverse effects except for major bronchodilative or anti-inflammatory effects, anti-allergic agents such as histamine receptor antagonists, leukotriene receptor antagonists, thromboxane synthetase inhibitors/receptor antagonists were developed. However, there are insufficient data about their clinical advantages in the long-term management of asthma, and then the development of more potent anti-inflammatory agents and further clinical evaluation is expected.

It is suggested that late-onset asthmatic response after the immunochallenge is associated with airway inflammation. Two kinds of asthmatic responses are observed immediate after the antigen-challenge and several hours following that. The early reaction is refered as immediate asthmatic response(IAR) and following phenomenon as late asthmatic response(LAR). IAR has been recognized by airflow limitation which results from acute bronchoconstriction due to allergen exposure, while LAR

is due to airway inflammation in the airway. The airway inflammation, characterized usually by extensive infiltration of cosinophils, mast cells and mononuclear cells, causes edematous swelling of the airway wall with or without smooth muscle contraction. Those pathologic changes would be related not only to LAR but also to airway hyperreactivity and aggravating asthma (Metzger, W.J., Hunninghake, G.W. and Richardson, H.B.: Late Asthmatic Responses; Inquiry into Mechanism and Significance, Clin. Rev. Allergy 3:145,1985). The mechanism of this pathological feature has not been elucidated fully.

Accordingly, it is desired to develop an agent for treating bronchial asthma which exhibits the excellent efficacy similar to that of adrenal cortex hormones, which simultaneously suppresses both immediate asthmatic responses and late asthmatic responses, and which is safe.

It is known that 2-phenyl-1,2-benzoisoselenazole-3(2H)-one (non-proprietary name: ebselen), a typical compound used in the present invention, has strong lipoxygenase inhibitory activity (Peter Kuhl et al., Prostaglandins, 31(1986), 1029-1048). However, it has never been reported as to whether ebselen is effective in the treatment of asthma.

Under the above circumstances, the present inventors carried out extensive studies, and found that the compounds represented by the formula (1) or (1') described below are highly effective in suppressing asthmatic responses, especially late asthmatic responses, in bronchial asthma.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides a therapeutic agent for treating asthma comprising, as an active component, a compound represented by the following formula (1) or (1') or a pharmaceutically acceptable salt of the compound:

wherein each of R^1 and R^2 independently represents a hydrogen atom, a halogen atom, a trifluoromethyl group, a nitro group, C1-C6 alkyl group or C1-C6 alkoxyl group, or R^1 and R^2 may be linked to each other to form a methylenedioxy group; R^3 represents an aryl group, an aromatic heterocyclic group, a 5- to 7- membered cycloalkyl group, or a 5- to 7-membered cycloalkenyl group, wherein the aryl group, aromatic heterocyclic group, cycloalkyl group, and the cycloalkenyl group may have a substituent; R^4 represents a hydrogen atom, a hydroxyl group, an -S-glutathione group, an -S-α-amino acid group, or an aralkyl group which may have a substituent at its aryl moiety; R^5 represents a hydrogen atom or a C1-C6 alkyl group; or R^4 and R^5 may be linked to each other to form a single bond; Y represents an oxygen atom or a sulfur atom, n represents an integer of 0 to 5 inclusive, and the selenium atom may be oxidized.

BRIEF DESCRIPTION OF A DRAWING

Fig. 1 shows effects of suppressing effect of ebselen on asthmatic responses of evselen on guinea pigs having antigen-induced asthma.

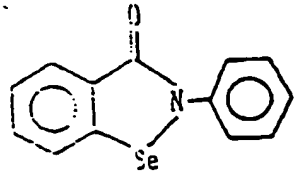
DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

In the present invention, agents for treating asthma include drugs which are used for the treatment of asthma

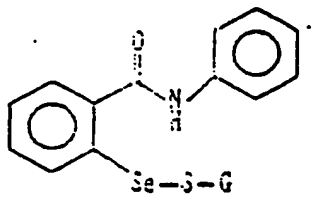
with the expectation of improving asthmatic conditions and preventive treatment.

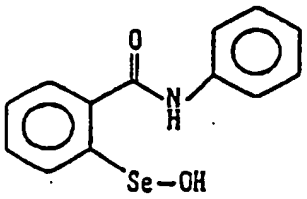
Compounds used as an active component of the agents for treating asthma are represented by the aforementioned formula (1) or (1') (hereinafter referred to as compound (1) or (1')). Examples of the C1-C6 alkyl group represented by R^1 include methyl group, ethyl group, propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, and pentyl group. Examples of the C1-C6 alkoxyl group include methoxyl group, ethoxyl group, and propoxyl group. Examples of the aryl group represented by R^3 include phenyl group; examples of the cycloalkyl group include cyclopentyl group, cyclohexyl group, and cycloheptyl group; examples of the cycloalkenyl group include 1-cyclopentenyl group, 1-cyclohexenyl group, and 1-cycloheptenyl group; and examples of the aromatic heterocyclic group include 5- or 6- membered aromatic heterocyclic groups such as pyridyl group, pyrimidyl group, imidazolyl group, oxazolyl group, isoxazolyl group, thiazolyl group, and furyl group. These groups may have substituents. Examples of the substituents include C1-C6 alkyl group, C1-C6 alkoxyl group, halogen group, carboxyl group, and hydroxyl group. The number of substituents is preferably 1 to 3. Of R^4 groups, the -S-glutathione group indicates a group formed by removing a hydrogen atom from the thiol moiety of glutathione; and the -S-?-amino acid group indicates a group formed by removing a hydrogen atom from the thiol moiety of thiol-containing ?-amino acid. Examples of the aralkyl group include benzyl group. R^4 and R^5 preferably form a

single bond. Particularly preferably, the compound of the present invention is 2-phenyl-1,2-benzoisoselenazole-3(2H)-one represented by the following formula:

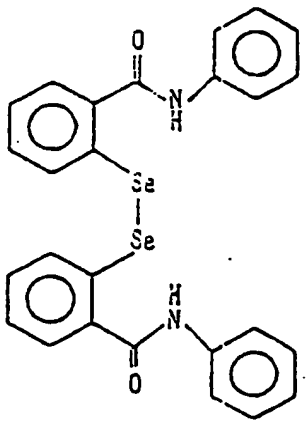


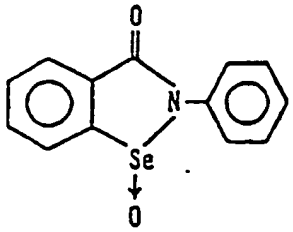
These compounds represented by the following formulas which are considered to be active metabolites of the above compound are also preferred.





(-S-G denotes a -S-glutathine group)





Moreover, in the present invention, pharmaceutically acceptable salts derived from these compounds may also be used.

The above-described compounds (1) or (1') are already known. They can be prepared, for example, in accordance with a method described in Japanese Patent Application Laid-open (kokai) Nos. 59-42373, 57-67568, 59-39894, 60-226868, 61-30963, or in Biochemical Pharmacology Vol. 3, No. 20, 3235-3239 and 3241-3245 (1984).

Compounds (1) or (1') and pharmaceutically acceptable salts thereof exhibited excellent effects of suppressing immediate and late asthmatic responses in bronchial asthma, particularly late asthmatic responses, as shown in the test example described below. Also, as a result of a toxicity test using mice and rats to which the compounds were administered orally or intraperitoneally, it was found that the compounds are very safe as evidenced by the LD_{50} (mg/kg) values shown in Table 1. Moreover, even after the compounds were administered at high doses, no side effects that might cause serious problems were observed.

Table 1

Animal	Administration route	LD_{50} (mg/kg)
Mouse	p.o.	> 6810
	i.p.	740
Rat	p.o.	> 6810
	i.p.	580

The agents for treating asthma according to the present invention may be formulated into various forms of drugs for oral and parenteral use such as tablets, capsules, powders, fine granules, liquids, suspensions, emulsions, dry syrups, inhalants, injections, and suppositories. Such drugs are prepared using a routine method by adding, to compound (1) or (1') or to a pharmaceutically acceptable salt thereof, lubricants, disintegrants, binders, and vehicles.

The dose of compound (1), (1') or of a pharmaceutically acceptable salt thereof varies depending on the administration route, condition of the patient, body weight of the patient, etc. In the case of oral administration to adults, it is usually 100-2,000 mg/day, and preferably 200-1,000 mg/day.

As described above, the agents of the present invention suppress both immediate and late asthmatic responses in bronchial asthma. Particularly, the agents exhibit remarkable effects on late asthmatic responses. Moreover, agents of the invention have low toxicity and thus are quite safe to humans.

Examples:

The present invention will next be described by way of examples, which should not be construed as limiting the invention.

Test Example:

Effects of ebselen were investigated using guinea pigs

having antigen-induced asthma by checking pulmonary functions under consciousness and spontaneous respiration.

<Methods>

(1) Animals

Each of female Hartley guinea pigs (SLC) (4 weeks old, body weight: approximately 250-300 g) was pretreated with cyclophosmide (2 mg/kg). After 2 days, ovalbumin (OA, 1 mg) and aluminum gel (1g) were injected intraperitoneally. Three weeks thereafter, OA (0.1 mg) and aluminum gel (1 g) were again injected intraperitoneally. The thus-treated guinea pigs were used as sensitized animals. At the time of testing, guinea pigs had grown to 11 weeks old and had body weights of 450-580 g.

(2) Apparatus and tools

· Pressure-type body pressismograph

· Pulmotacograph (TP-601G, Nippon Kodensha)

· Differential transducer (T-601, Nippon Kodensha)

· Gas flow resistor tube (Lilly type, Nippon Kodensha)

· Oscilloscope (DS-9121, Iwasaki Tsushinki)

· Computer (Macintosh Centris 660AV, Apple)

· Software (created for analyzing respiration based on LabView for Macintosh 3.01)

· Nebulizer (NE-U10, Tateishi Denki)

(3) Methods for administering agents and for exposing to antigens:

· Groups of guinea pigs pretreated with dexamethasone: Dexamethasone (1 mg/kg) was dissolved in 100% DMSO (1

ml), and the solution was infected intraperitoneally for 4 consecutive days. The last intraperitoneal injection was performed 24 hours prior to the exposure to antigens.

· Groups of guinea pigs pretreated with ebselen:

Evselen (5 mg/kg) was dissolved in 100% DMSO (1 ml), and the solution was injected intraperitoneally 30 minutes before exposure to antigens.

· Control groups:

100% DMSO (1 ml) was injected intraperitoneally 30 minutes before exposure to antigens.

· Method for exposing to antigens:

OA (40 mg) was dissolved in physiologic saline (4 mg/ml), and the solution was inhaled for 2 minutes using an ultrasonic nebulizer.

(4) Method for checking pulmonary functions:

In accordance with a method of Agrawal (Agrawal, K.P.; Specific Airway Conductance in Guinea Pigs: "Normal Values and Histamine Induced Fall", Respiratory Physiology 43: 23, 1981), each guinea pig was fixed on a pressure-type body pressismograph, and %variation of specific airway conductance (sGaw) was measured. Air flow through the nose and changes of internal pressure of the box were monitored. Respective wave forms were digital-sampled at 1024 Hz, and dots from the end expirium to the start of inspirium were reverted to a regression line. Using the inclination (tan) of the regression line, sGaw was obtained. sGaw data was measured before exposure to antigens. After physiologic saline was inhaled for 2 minutes, sGaw was measured again to

confirm that the data had no change. The value at this time was taken as 100%, and %variation of sGaw after exposure to antigens was obtained.

The results are shown in Fig. 1. In groups of guinea pigs pretreated with ebselen, both immediate and late asthmatic responses were more effectively suppressed than those in guinea pigs of control group.

When ebselen pretreatment groups are compared with dexamethasone pretreatment groups, the levels of suppression of immediate asthmatic responses were almost equal. However, late asthmatic responses were significantly suppressed in ebselen pretreatment groups, almost perfectly suppressing late asthmatic responses which were observed at between 180 and 420 minutes in the control group.

In this connection, the dexamethasone dose of 1 mg/kg for 4 days to a guinea pig is estimated to be a dose of 240 (60 mg x 4 days) mg of dexamethasone to a human (body weight: 60 kg). This amount of dexamethasone is equal to 2400 mg of prednisolone (0.5 mg of dexamethasone is equivalent to 5 mg of prednisolone).

This amount of prednisolone (2400 mg) is equivalent to the amount consumed in a pulse therapy in which 1 g/day of prednisolone is consecutively administered for 3 days.

As is understood from the above, ebselen gives more excellent effects than do therapies adopted in current clinical situations.

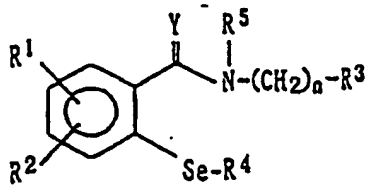
Example 1:

Tablets

Tablets having the following composition were prepared using a known method.

Ebselen	50 mg
Carboxymethylcellulose	25 mg
Starch	5 mg
Crystalline cellulose	40 mg
Magnesium stearate	2 mg
Total	122 mg

The present invention provides a safe therapeutic agent for asthma which suppresses both immediate and late asthmatic responses in bronchial asthma. The therapeutic agent of the invention comprises, as an active component, a compound represented by the following formula (1) or (1'):



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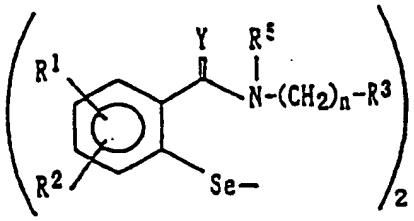

(1')

or a pharmaceutically acceptable salt of the compound. The agent of the invention shows highly effects on both immediate and late asthmatic responses, and particularly on late asthmatic responses. The agent can be safely administered to humans as it has low toxicity.

The claims defining the invention are as follows:

1. The use of 2-phenyl-1,2-benzoisoselenazole-3(2H)-one or a pharmaceutically acceptable salt thereof, for producing a therapeutic agent for the treatment of bronchial asthma.

2. The use of 2-phenyl-1,2-benzoisoselenazole-3(2H)-one or a pharmaceutically acceptable salt thereof, for producing a therapeutic agent for suppressing late asthmatic responses in bronchial asthma.

3. A method for the treatment or prophylaxis of asthma in a mammal requiring said treatment or prophylaxis, which method includes or consists of administering to said mammal an effective amount of 2-phenyl-1,2-benzoisoselenazole-3(2H)-one or a pharmaceutically acceptable salt thereof.

4. The method of claim 3 wherein the asthma is bronchial asthma.

5. The method of claim 3 wherein the treatment is suppression of late asthmatic responses in bronchial asthma.

6. 2-Phenyl-1,2-benzoisoselenazole-3(2H)-one when used in the treatment or prophylaxis of asthma.

Dated 15 June, 2000
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Fig. 1